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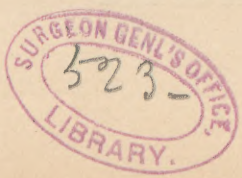
The blood in malarial fever has of late years offered a rich field for investigation, and many have been the articles and reports upon the subject since the discovery of the malarial parasite. These investigations have, however, been limited almost entirely to the malarial organism and the changes it brings about in the red corpuscles. Little attention has been paid to the leucocytes, and the literature on this part of the subject is scanty. The work done has been confined chiefly to the pigmented leucocytes which occur in the blood in malarial fever—a question which does not concern us.

Rieder, in his work on the leucocytoses, refers briefly to the fact that Kelsch, Von Limbeck, Fahrmann and others have found no leucocytosis in malarial fever. Indeed, one or two of them state that the number of the leucocytes falls below normal.

Kelsch (Arch. de Physiol., 1875, p. 690, and 1870, p. 490) found the leucocytes diminished from one-third to one-half in malarial fever. He also states that at the beginning of the paroxysm there is a slight transient increase in the number of leucocytes in the blood. He found that the minimum number of the leucocytes corresponded to the maximum enlargement of the spleen, and that when the size of the spleen was diminished by means of an electrical current, there was a transient increase in the number of the leucocytes.

The most exhaustive article on the subject is that of Bastianelli (Bull. d. Real. Accad. Med. d. Roma, Ann. xviii, Fasic. v, p. 487). He occupies himself chiefly with the discussion of the pigmentation of leucocytes and phagocytosis. He refers to Golgi, who holds that phagocytosis occurs regularly as a function of the leucocytes, obtaining at definite phases of development of the organism. This phagocytosis is accomplished both by the polynuclear leucocytes and the large mononuclear and transitional forms, while the lymphocytes and eosinophiles never contain pigment. Golgi also believes that phagocytosis may account for the spontaneous recovery observed in so many cases, and that it plays an



important part in the prevention of all malarial fevers from becoming pernicious.

Bastianelli finds:

1. The number of leucocytes is always diminished in malarial fever.

2. The number of pigmented leucocytes increases markedly at the time of sporulation of the organism in the tertian cases; *i. e.*, at the beginning of the febrile paroxysm.

3. In cases of spontaneous recovery no increase is to be observed in the number of pigmented leucocytes. This phenomenon of phagocytosis may occur at all stages of the cycle of evolution of the organism in the æstivo-autumnal cases.

4. The phagocytic leucocytes rapidly become necrotic and disappear from the blood. This probably accounts for the diminution in number of the leucocytes which takes place in malarial fever.

5. The phagocytosis is accomplished chiefly by the large mononuclear forms.

As regards the relative numerical proportions of the various forms of leucocytes, he only states that in post-malarial anæmia the percentage of the polynuclear elements decreases, while that of the lymphocytes and large mononuclear elements increases.

The observations here reported were undertaken with the view of determining, if possible, whether any regular variations took place in the number of leucocytes in the blood during the febrile and afebrile periods of malarial fever.

Malaria is very prevalent in the immediate neighborhood of Baltimore, and we see three types of fever, as follows:

1. The spring or tertian type. This is most common in the spring and early summer, though cases are often seen in the autumn. The paroxysms occur every other day if the case be one of single tertian, and daily if it be one of double tertian; *i. e.*, with two sets of organisms in the blood, maturing on alternate days. This latter form is the commonest type we see here.

2. The quartan type. This is rarely seen, there being only five cases on record in the hospital. The paroxysms are rarely as severe as those in the previously mentioned type of the disease. They may occur every third day, two out of every three days, or every day, according as there may be one, two or three sets of organisms in the blood.

3. The fall type. This is the æstivo-autumnal type of the Italian observers, and occurs in the late summer and fall. The course of the fever is irregular. There may be definite paroxysms, as in the tertian type of the disease, or the temperature may be continuously elevated for days. The paroxysms may occur daily, or there may be no regular periodicity.

The counts were made with the Thoma-Zeiss hæmocytometer, the same instrument being used in each case. Care was taken that the counts should not be made within two hours after meals. In about half the cases the large one to twenty mixer was used, with the one-third per cent acetic acid solution as a diluting medium. In the remainder the smaller one to one hundred mixer was used, with Toison's fluid as a diluent. The results obtained with the latter instrument seem fully as accurate as those with the former. Four whole fields were counted in each case.

The relative numerical proportions of the various forms of leucocytes were estimated by means of dried and stained cover-glass preparations. These were hardened by heat according to Ehrlich's method, and stained with the Ehrlich-Biondi triple stain as modified by Thayer. The counting was done with a mechanical stage, and the number of leucocytes counted varied. In all cases at least two hundred and fifty were counted, and in one or two as many as one thousand. The nomenclature used is according to Thayer, which is a modification of those used by Ehrlich and Uskow. The lymphocytes and small mononuclear forms of Ehrlich are given together under the head of small mononuclears, while the large mononuclear and transitional forms are classified together as large mononuclears. It is difficult to draw any hard and fast line between these two groups. Any mononuclear element one and one-half times as large as a red blood corpuscle was counted as a large mononuclear. According to this rule a large lymphocyte would be occasionally classified among the large mononuclears, while on the other hand the small transparent forms of Uskow would be counted among the small mononuclears. The difference was never more than one per cent, however.

The cases have been tabulated for convenience sake, and as little superfluous matter added as possible.

No.	Patient.	Date Admitted. — Previous Duration.	Type of Organism.	Date.	Hour.	Temperature.	Leucocytes per cmm.	Remarks.	Per cent. Polynuclears.	Per cent. small Mononuclears.	Per cent. large Mononuclears.	Per cent. Eosinophiles.
1.	K.—Male, 26. White.	August 18, 1893. Illness began August 16, 1893. Daily paroxysms.	Tertian (double).	Aug. 18.	1 P. M.	104.2°	3250	Beginning of chill.	68.2	15.1	15.6	1.1
					4 P. M.	103 6°	6000	.....	73.2	11.9	14.1	.8
					6 P. M.	101.6°	4100	.....	62.4	15.2	20.3	2.1
					12 mid.	97.8°	2000	.....	54.7	20.5	23.8	1.
2.	M.—Male, 33. White.	August 16, 1893. Illness began August 11, 1893. Daily paroxysms.	Tertian (double).	Aug. 19.	1.45 P. M.	101°	5500	Beginning of chill.	71.3	17.4	11.1	.2
				Aug. 20.	10 A. M.	97.2°	4500	.....	68.	7.3	24.2	.5
					10 P. M.	103°	2666	Chill began at 2 P. M.	52.7	12.8	33.2	1.3
				Aug. 21.	9 A. M.	97°	2500		49.8	18.6	30.9	.7
3.	S.—Male, 17. White.	August 21, 1893. Illness began August 14, 1894. Paroxysms every other day.	Tertian (single).	Aug. 23.	9 A. M.	100.2°	6000	Beginning of chill.	82.1	12.1	5.1	.7
					10 A. M.	103.6°	7750	.....	..	..	..	..
					11 A. M.	103.2°	7500	.....	75.8	7.1	16.	1.1
					12 M.	102.6°	4750	Sweating.	..	..	..	..
					1 P. M.	100.1°	5000	.....	..	..	..	..
					4 P. M.	99°	3500	.....	66.	22.4	10.6	1.
				Aug. 24.	12 M.	98°	3750	.....	65.1	23.7	9.2	2.
4.	Same case.	.....	.....	Aug. 25.	8 A. M.	102°	7250	Beginning of chill.	78.1	12.4	7.4	2.1
					10 A. M.	104.8°	9750	.....	79.2	8.1	12.4	.3
					12 M.	102°	6250	Sweating.	70 8	15.1	13.7	.4
					2 P. M.	100°	6000	.....	64.	13.5	21.5	1.
					4 P. M.	98.6°	5250	.....	..	..	..	..
					8 P. M.	98.6°	5000	.....	63 2	22.	8.8	6.
5.	S.—Male, 20. White.	August 24, 1893. Illness began August 10, 1893. Daily paroxysms.	Tertian (double).	Aug. 24.	8 P. M.	98.6°	3000		63.1	21.8	14.	1.1
					11 P. M.	105°	2250	Beginning of chill.	75.2	14.	10.2	.6
					12 P. M.	105°	3000	.....	..	..	..	..
				Aug. 25.	1 A. M.	104.9°	4200	.....	..	..	..	..
					2 A. M.	104.7°	6750	.....	74.6	7.5	17.4	.5
					3 A. M.	103.9°	4500	Sweating.	..	..	..	..
					4 A. M.	103.2°	3250	.....	..	..	..	..
					5 A. M.	102.4°	3500	.....	66.8	17.	16.	.2
					6 A. M.	101.1°	3000	.....	..	..	..	..
					8 A. M.	98.4°	2600	.....	70 2°	20.6	7.	.2
6.	B.—Male, 20. White.	August 25, 1893. Illness began August 20, 1893. Daily paroxysms.	Tertian (double).	Aug. 26.	8 A. M.	98°	6000	Just before chill.	66.9	22.1	10.2	.8
					2 P. M.	105°	8250	.....	71.	13 8	14 1	1.1
					6 P. M.	99°	4100	Sweating.	61.3	15.7	22.6	.4
				Aug. 27.	8 A. M.	98.6°	2000	.....	50.4	20.4	29.2	.0

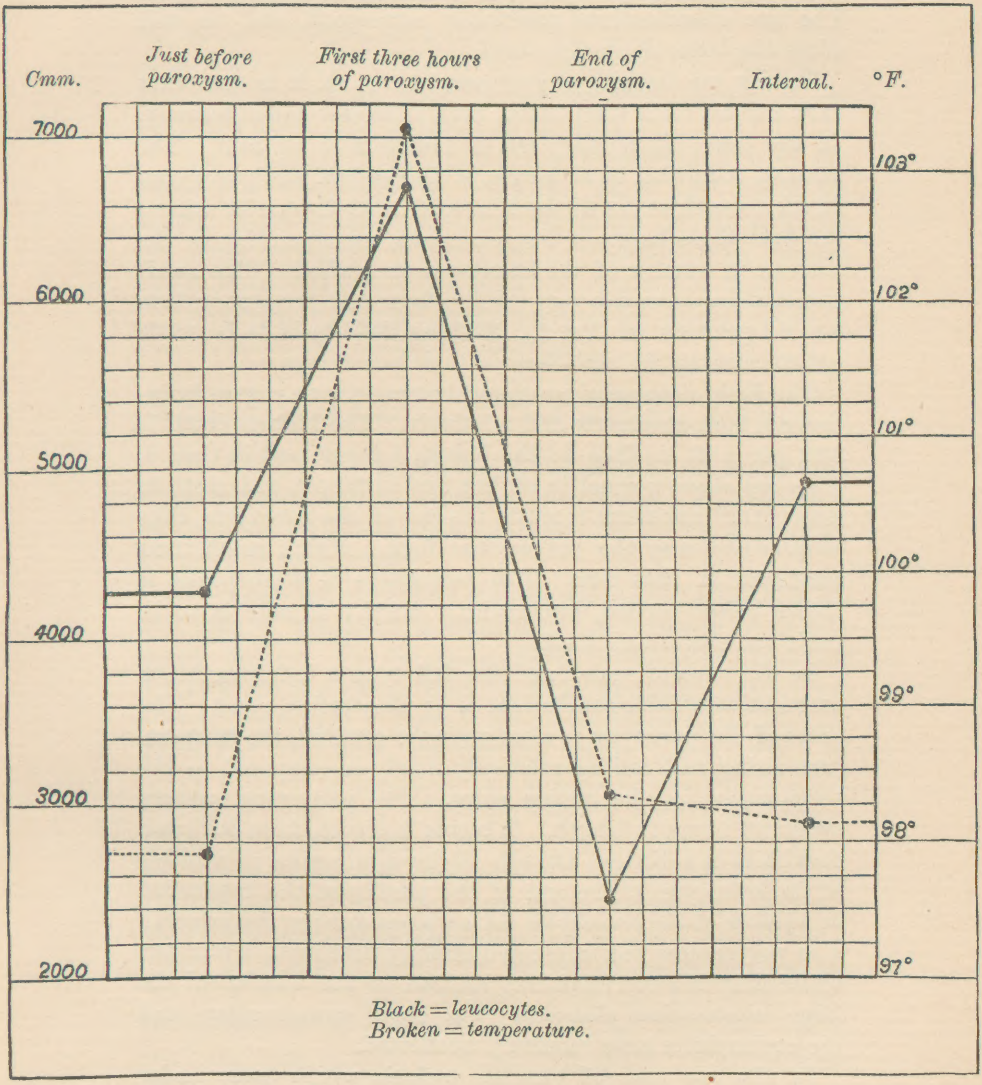
7.	P.—Male, 19. White.	August 28, 1893. Illness began August 25, 1893. Daily paroxysms.	Tertian (double).	Aug. 29.	10 P. M.	97.8°	5000	Just before chill.	70.6	14.5	13.8	1.1
					12 P. M.	104.2°	6666	.....	81 6	6.4	11.1	.9
				Aug. 30.	12 M.	97°	2100	.....	61.4	17.4	19.2	2.
8.	W.—Male, 27. White.	March 6, 1894. Illness began March 4, 1894. Daily paroxysms.	Tertian (double).	March 6.	1.15 P. M.	103°	5000	Beginning of chill.	73 2	8.	18.8	.0
					4.15 P. M.	105°	6250	.....	80.2	6.9	12.6	.3
				March 7.	8.30 A. M.	97.9°	1500	.....	43.2	26.	30.4	.4
				March 8.	9 A. M.	98°	3100	.....	48 8	27.2	13.	2.
				March 9.	11 A. M.	98.6°	5750	.....	60.8	30.1	8.9	.2
				March 10.	11.30 A. M.	98.6°	5200	.....	74.1	20.9	4.2	.8
9.	G.—Male, 22. White.	August 14, 1894. Illness began August 9, 1894. Daily paroxysms.	Tertian (double).	Aug. 15.	3.30 P. M.	100°	3500	Beginning of chill.	73.8	13.	12.1	1.1
					10 P. M.	101°	1500	.....	64.1	14.1	21.	.8
				Aug. 16.	8 A. M.	98°	5000	.....	55.2	21.3	23.3	.2
					2.30 P. M.	98°	3000	Just before chill.	51.6	25.2	19.1	4.1
10.	J.—Male, 48. Black.	August 14, 1894. Illness began August 6, 1894. Daily paroxysms.	Tertian (double).	Aug. 16.	12 M.	98.6°	5100	.....	50.2	28.7	20.	1.1
				Aug. 17.	2 P. M.	101°	7000	Beginning of chill.	81.5	8.	10.	.5
					5 30 P. M.	100.6°	5750	Sweating.	72.8	9.1	17.1	1.
					10 P. M.	98°	2000	.....	58.	13.5	28.	.5
11.	B.—Female, 13. White.	August 24, 1893. Illness began August 14, 1893. Irregular fever since that date.	Æstivo-autumnal.	Aug. 27.	8 P. M.	103.2°	4500	Temperature not normal since admission.	62.8	27.6	9.6	.0
				Aug. 28.	8 P. M.	101.7°	2200		69.9	20.4	9.5	.2
				Aug. 30.	8 P. M.	98.2°	3500	First normal temperature.	63 1	7.1	29.6	.2
12.	T.—Male, 8. White.	September 2, 1893. Illness began August 12, 1893. Irregular fever since that date.	Æstivo-autumnal.	Sept. 3.	10 A. M.	99.8°	6100	Irregular fever: temp. not touching normal for 3 days, *i. e.*, until the 5th.	54.1	22.	22.1	.1
					6 P. M.	102°	4200		69.2	18.	11.3	1.5
				Sept. 4.	4 P. M.	104.6°	5200		48.1	20.2	31.3	.4
				Sept. 5.	8 A. M.	99.2°	6500		65.5	19.9	13.6	1.
13.	C.—Male, 30. Black.	September 11, 1893. Illness began September 6, 1893. Irregular fever with night sweats.	Æstivo-autumnal.	Sept. 11.	4 P. M.	105°	6400	Height of febrile paroxysm lasting 24 hours.	72.1	16.7	11.2	.0
				Sept. 12.	8 A. M.	98.8°	3500		70.6	12.4	13.9	3.1
					6 P. M.	98.6°	4000		68.7	12.7	18.1	.5
14.	C.—Male, 27. White.	September 16, 1893. Illness began August 7, 1893. Irregular febrile paroxysms with sweating.	Æstivo-autumnal.	Sept. 17.	8 A. M.	98.6°	2100		65 3	12.7	20.6	1.4
					8 P. M.	101.4°	2500	Height of paroxysm lasting 20 hours.	68.7	18.6	12.1	.6
				Sept. 18.	12 M.	98.6°	3400		59.	24.7	16.1	.2
15.	M.—Male, 26. White.	August 16, 1894. Illness began August 12, 1894. Irregular febrile paroxysms with chills and sweating.	Æstivo-autumnal.	Aug. 16.	3.30 P. M.	101°	5150	Temp. falling.	69.6	13.1	16.2	1.1
				Aug. 17.	10 A. M.	99°	6750	Temp. began to rise at 2 P. M.	52.5	23.5	23.	1.
					5 P. M.	100.7°	4200		45.1	23.7	30.	1.2
16.	K.—Male, 12. White.	July 19, 1894. Previous history not obtainable.	Quartan.	July 21.	8 A. M.	98.4°	5500		59.1	24.9	15.7	.3
					8 P. M.	100.5°	5100	Height of slight paroxysm.	61.3	17.8	18.3	2.6
				July 22.	8 A. M.	98.6°	5200		66.	17.2	16.1	.7

In looking over the table of tertian cases it is striking to note the uniform diminution in number of the leucocytes during the febrile paroxysm [leucocytolysis?]. It is also to be noted that the maximum number of leucocytes is found as a rule two or three hours after the chill. From that time on there is a progressive diminution until the minimum number of leucocytes is reached at the end of the paroxysm when the temperature is subnormal, which it usually is for some hours. The number of leucocytes then rises somewhat, and during the interval occupies a position about midway between the maximum and minimum above mentioned. The increase at the beginning of the paroxysm does not take place until after the chill, as the average number of leucocytes just before the chill is very slightly higher than the average number during the interval. These points are well shown if the average number of leucocytes at the different stages of the paroxysm be represented graphically together with the average temperature at those times. (See chart.)

The strong objection to the occurrence of this apparently regular oscillation of the number of leucocytes is the fact that the differences involved are so extremely small as to almost come within the limit of error of the hæmocytometer. This may be placed at two thousand at the outside, if sufficient care be taken. While we may be in doubt as to the occurrence of an increase in the number of leucocytes in the blood at the beginning of the malarial paroxysm, there can be little doubt that there is a definite diminution in the number of the leucocytes toward the end of the paroxysm. The difference between the average maximum and the average minimum number of leucocytes is 4271, which is well outside of the limit of error. The average number of leucocytes three hours after the beginning of the paroxysm is only 2300 more than the average number just before the beginning of the paroxysm. Yet this increase, slight as it may be, occurs in seven of our ten cases, and until proof to the contrary be offered, we are justified in thinking it to take place regularly.

The relative numerical proportion of the various forms of leucocytes is stated by Ehrlich to be as follows:

Polynuclears, 70 to 75 per cent; lymphocytes, 15 to 25 per cent; mononuclear and transitional forms, 6 per cent, and eosinophiles, 1 to 5 per cent.


Cmm.
Just before paroxysm.
First three hours of paroxysm.
End of paroxysm.
Interval.
°F.
7000
6000
5000
4000
3000
2000
103°
102°
101°
100°
99°
98°
97°
Black = leucocytes.
Broken = temperature.

Uskow gives it as follows: Lymphocytes and small mononuclears, 18 per cent; transparent and transitional forms, 6 per cent, and polynuclears and eosinophiles, 76 per cent. The two classifications practically correspond, and we will adopt the latter as our standard.

Taking up first the polynuclear leucocytes, it is seen that they are markedly diminished, both relatively and absolutely. In one case (No. 8) they are as low as 43.2 per cent. The greatest reduction is, as a rule, at the end of the paroxysm. In six cases there is a distinct increase in their number during the first three hours of the paroxysm, corresponding to the increase in number of the leucocytes as a whole. The small mononuclear elements vary widely, from 30.1 per cent in Case 8 to 6.4 per cent in Case 7. Nothing definite is to be made out concerning the variations in their percentage.

The large mononuclear elements are, as a rule, greatly increased, both absolutely and relatively. The highest count is 33.2 per cent in Case 2; the lowest, 4.2 per cent in Case 8. They are above normal in all but two instances, and seem to reach their maximum towards the end of the paroxysm, thus counterbalancing the polynuclear forms, which reach their minimum at that time. The percentage of eosinophiles is rather below normal, but nothing worthy of note is to be made out concerning them.

In the cases of malaria of the fall type it is impossible to arrive at as definite conclusions as in the tertian cases. The onset of the paroxysm is almost always gradual, the temperature rising and falling relatively slowly as compared to the temperature in the tertian cases. The paroxysms average about 36 hours in length. It seems, however, from our cases that there is a distinct though slight diminution in number of the leucocytes at the end of the paroxysm, the reparation in number of the leucocytes taking place during the interval. The polynuclear elements are distinctly decreased in number, while there is a corresponding increase in the number of the large mononuclear elements. The small mononuclears and the eosinophiles seem relatively unaffected.

In the one case of quartan malaria which came under observation, no variations in number of the leucocytes could be made out. The differential count of the leucocytes, how-

ever, showed the same condition of affairs already noted in the tertian and fall cases.

Besides the observations here reported, a sufficient number of extra counts were made to bring the total number of counts up to one hundred, the average result being 4323. So that if we take 7000 per cmm. as the average normal number of leucocytes in human blood, in malarial fever there is on an average a diminution of about 38 per cent.

This is possibly to be explained as Bastianelli says, by the necrosis of the phagocytic leucocytes which have taken up altered blood pigment, malarial organisms and degenerated red blood corpuscles. At any rate the diminution in number of the leucocytes does occur, whatever may be the cause.

The average numerical proportions of the various forms of leucocytes in the 16 cases are as follows:

Polynuclears.	Small Mononuclears.	Large Mononuclears.	Eosinophiles.
65.04 per ct.	16.9 per cent.	16.9 per cent.	0.96 per cent.

The increase in the number of the polynuclear forms just after the chill is to be explained possibly as a manifestation of chemotaxis due to toxines circulating in the blood, or as an evidence of regeneration.

The confusion of typhoid with malarial fever, especially the fall type of the latter, is something that we must be on our guard against. In the latter form of malarial fever the temperature is often elevated for days, the patient is dull and listless, the tongue is heavily coated, the spleen is readily palpable, and Ehrlich's diazo-reaction occurs in the urine. In short, with the exception of the absence of the diarrhœa and rose-spots, there is a tolerably complete picture of typhoid fever. In Cases 11 and 12 the temperature remained elevated for four and three days respectively. The organisms of this type of malarial fever are very easily overlooked. For the first week or so after the beginning of the illness the only forms of organism present in the peripheral circulation are the so-called "hyaline" bodies. These are very small, and to one unaccustomed to examining malarial blood are readily confused with vacuoles in the red corpuscles. The crescentic forms of the organism do not appear until later in the disease, and the segmenting forms are not found in the peripheral circulation.

Uskow has called attention to the fact that in typhoid fever there is no leucocytosis, and that there is a diminution in the percentage of the polynuclear leucocytes with a corresponding increase in the percentage of the large mononuclear forms. This he believes to occur regularly in uncomplicated cases of typhoid fever, and his statement has been verified by a number of counts made by Dr. W. S. Thayer and myself at the Johns Hopkins Hospital. But this condition of the blood is exactly the same as the one which obtains in malarial fever of the fall or æstivo-autumnal type. So that the estimation of the number of leucocytes, and the determination of the proportions of the various forms by means of stained specimens, are not sufficient for the diagnosis of typhoid unless we can definitely rule out the presence of malarial organisms.

In conclusion, a few words may be added about the leucocytes in malarial anæmia.

While the occurrence of a leucocytosis in most secondary anæmias is the rule, it is never very marked, rarely being above 15 to 18,000. In four cases of malarial anæmia which we have had under observation the increase in the number of leucocytes was striking. In two cases where the red corpuscles ranged just above 3,000,000 per cmm. the leucocytes were 28,000 and 30,000 respectively. In another case the red corpuscles were just under 2,000,000, while the leucocytes reached 40,000. In the fourth case the red corpuscles were 3,600,000, a relatively mild anæmia, while the leucocytes ranged above 20,000 for a week. In all four cases the increase was solely in the polynuclear leucocytes.